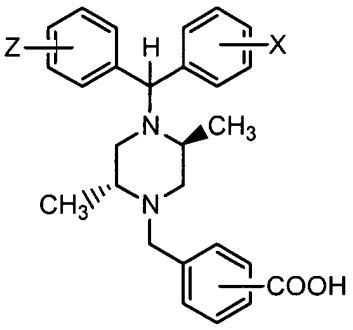
THE CLAIMS

We claim:

1. A therapeutic composition for combating ischemic damage, the composition comprising an effective amount of a diarylmethylpiperazine compound of the general formula:



(1)

wherein:

Z is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above; and

X is selected from the group consisting of hydrogen, hydroxyl, halogen and alkoxy,

or a pharmaceutically acceptable ester or salt thereof.

2. The composition according to claim 1, wherein the composition further comprises an effective amount of a second compound used for treatment of a cardiac disorder.

3. The composition according to claim 2, wherein the second compound is selected from the group consisting of nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin.

4. The composition according to claim 2, wherein the second compound is administered contemporaneously with the diarylmethylpiperazine compound.

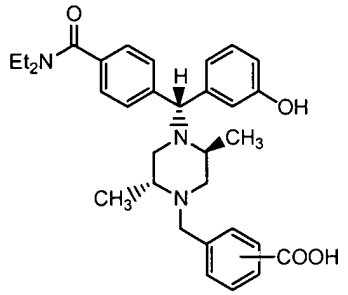
5. The composition according to claim 1, wherein the diarylmethylpiperazine compound is a non-analgesic compound.

6. The composition according to claim 5, wherein the diarylmethylpiperazine compound acts predominately on peripheral delta opioid receptors.

7. The composition according to claim 1, wherein the diarylmethylpiperazine compound is administered concurrently with the onset of an ischemic event; prior to onset of ischemia; pre-surgery; or after the onset of an ischemic event.

8. A method of reducing ischemic damage in a subject comprising:
administering an effective amount of the composition according to claim 1.

9. A therapeutic composition for combating ischemic damage, the composition comprising an effective amount of a non-analgesic diarylmethylpiperazine compound of the formula:



or a pharmaceutically acceptable ester or salt thereof.

10. The composition according to claim 9, wherein the composition further comprises a second compound used to mediate a protective or corrective cardiac response or activity.

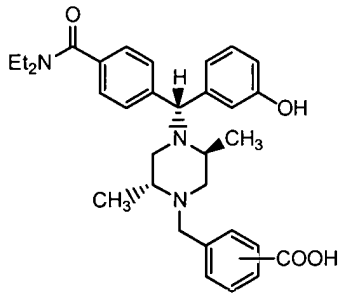
11. The composition according to claim 10, wherein the second compound is selected from the group consisting of nitrates, beta-adrenergic blockers, calcium channel

antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin.

12. The composition according to claim 10, wherein the second compound is administered contemporaneously with the diarylmethylpiperazine compound.

13. The composition according to claim 9, wherein the non-analgesic diarylmethylpiperazine compound is administered concurrently with the onset of an ischemic event; prior to onset of ischemia; pre-surgery; or after the onset of an ischemic event.

14. A method of reducing ischemic damage in a subject comprising: administering an effective amount of a therapeutic composition comprising a non-analgesic diarylmethylpiperazine compound of the formula:



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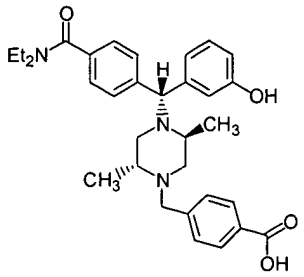
or a pharmaceutically acceptable salt or ester thereof.

15. A therapeutic composition for combating ischemic damage, the composition comprising an effective amount of a non-analgesic diarylmethylpiperazine compound of the formula:



or a pharmaceutically acceptable ester or salt thereof.

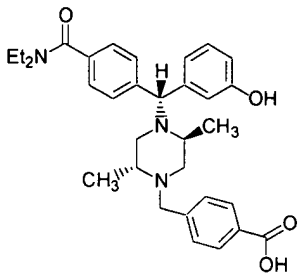
16. The composition according to claim 15, wherein the composition further comprises a second compound used to mediate a protective or corrective cardiac response or activity.

17. The composition according to claim 16, wherein the second compound is selected from the group consisting of nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin.

18. The composition according to claim 16, wherein the composition further comprises a pharmaceutically acceptable carrier.

19. The composition according to claim 15, wherein the diarylmethylpiperazine compound is administered concurrently with the onset of an ischemic event; prior to onset of ischemia; pre-surgery; or after the onset of an ischemic event.

20. A method of reducing ischemic damage in cardiac tissue, the method comprising: administering to said mammal an effective amount of a non-analgesic diarylmethylpiperazine compound of the formula:



or a pharmaceutically acceptable salt or ester thereof.

21. The method according to claim 20, wherein the diarylmethylpiperazine compound is administered multiple times concurrently with the onset of an ischemic event.

22. The method according to claim 20, wherein the diarylmethylpiperazine compound is administered to a subject as a preventive regime to prevent disease progression in an individual in the symptomatic phase of ischemic heart disease.

23. The method according to claim 20, wherein the diarylmethylpiperazine compound is administered after the onset of an ischemic event.

24. The method according to claim 20, further comprising administering a second compound that effectuates a protective or corrective cardiac response.

25. The method according to claim 24, wherein the second compound is selected from the group consisting of nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin.

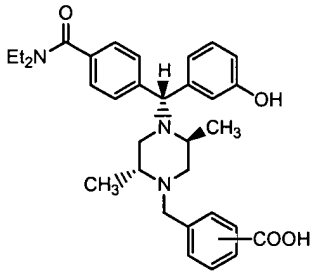
26. The method according to claim 24, wherein the second compound is administered contemporaneously with the diarylmethylpiperazine compound.

27. The method according to claim 20, wherein the diarylmethylpiperazine compound is administered by a mode of administration selected from the group consisting of

parenteral, non-parenteral, oral, rectal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, sublingual, oral mucosal, bronchial, lymphatic, and intra-uterine administration.

28. The method according to claim 20, wherein the mammal is a human.

29. A preserving solution for an isolated organ comprising a compound of the formula:



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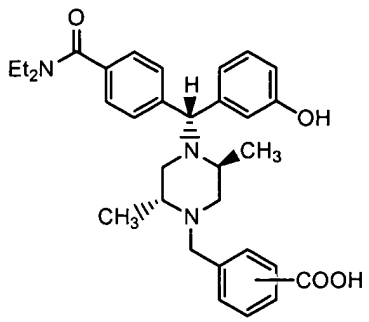
or a pharmaceutically acceptable salt or ester thereof.

30. The solution of claim 29, wherein the isolated organ is selected from the group consisting of heart, liver, kidney, cornea, lung and combination thereof.

31. A method of protecting against ischemia and reperfusion injury in a mammal comprising administering to the mammal an effective amount of a delta opioid receptor agonist of the formula:



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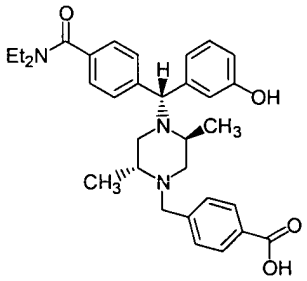
or pharmaceutically acceptable esters and salts thereof; and a second compound that effectuates an anti-ischemic effect.

32. The method of claim 31, wherein the second compound is arginine hydrochloride.

33. A method of effectuating ischemic preconditioning of cardiac tissue in a subject, the method comprising: administering to the subject an effective amount of a diarylmethylpiperazine compound of the formula:



or pharmaceutically acceptable esters and salts thereof.

34. The method of claim 33, wherein the compound is administered by a mode of administration selected from the group consisting of parenteral, non-parenteral, oral, rectal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, sublingual, oral mucosal, bronchial, lymphatic, and intra-uterine administration.

35. The method according to claim 33, further comprising administering a second compound that effectuates a protective or corrective cardiac response.

36. The method according to claim 35, wherein the second compound is selected from the group consisting of nitrates, beta-adrenergic blockers, calcium channel antagonists, ACE inhibitors, non-peptide angiotensin II antagonists, IIb/IIIa antagonists and aspirin.

37. The method according to claim 35, wherein the second compound is administered contemporaneously with the diarylmethylpiperazine compound.

38. A method of protecting against potential ischemia in a subject without inducing a receptor-mediated analgesia of the subject comprising administering an effective amount of the diarylmethylpiperazine compound of claim 33.

39. The method according to claim 38, wherein the subject is a human.

40. The method according to claim 39, wherein the diarylmethylpiperazine compound is orally administered.